**Corresponding author:** Ana Gabriela Maguitman
**Email:** anmaguit@cs.indiana.edu

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**Authors**: Ana G. Maguitman, Andreas Rechtsteiner, Karin Verspoor, Luis M. Rocha

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# LARGE-SCALE TESTING OF BIBLIOME INFORMATICS*

ANA G. MAGUITMAN[†], ANDREAS RECHTSTEINER[‡],
KARIN VERSPOOR[§], LUIS M. ROCHA[†]

[†]*School of Informatics, Indiana University*
*1900 East Tenth Street, Bloomington, IN 47408*
*E-mail: anmaguit@indiana.edu, rocha@indiana.edu*

[‡]*Center for Genomics and Bioinformatics, Indiana University*
*1001 East Third Street, Bloomington, IN 47405*
*E-mail: arechtsteiner@gmail.com*

[§]*Los Alamos National Laboratory*
*PO Box 1663, MS B256, Los Alamos, NM 87545*
*E-mail: verspoor@lanl.gov*

Literature mining is expected to help not only with automatically sifting through huge biomedical literature and annotation databases, but also with linking bio-chemical entities to appropriate functional hypotheses. However, there has been very limited success in testing literature mining methods due to the lack of large, objectively validated test sets or "gold standards". To improve this situation we created a large-scale test of literature mining methods and resources. We report on a specific implementation of this test: how well can the Pfam protein family classification be replicated from independently mining different literature/annotation resources? We test and compare different keyterm sets (MeSH terms, keywords extracted from PubMed abstracts, and Gene Ontology keyterms) as well as different algorithms for issuing protein family predictions. We find that protein families can indeed be automatically predicted from the literature. Using words from PubMed abstracts, of 3663 proteins tested, over 75% were correctly assigned to one of 618 Pfam families. For 90% of proteins the correct Pfam family was among the top 5 ranked families. For all tested algorithms, we also found that protein family prediction is far superior with keywords extracted from PubMed abstracts than with GO annotations. This suggests that although GO is becoming the standard annotation resource for gene and protein annotation, PubMed abstracts and even MeSH keyterms are far superior as resources for literature mining. Finally, we show that Shannon's entropy can be exploited to improve prediction by facilitating the integration of the different literature sources tested.

## 1. Introduction

Biology was until recently essentially a hypothesis driven science in which experiments were carefully designed to answer one or very few specific questions,

*All authors contributed equally to the work.

like the function of a specific protein in a specific context. In the last decade, fueled by the widespread use of high-throughput technology, we have witnessed the emergence of a more data-driven paradigm for biological research . This data-driven approach to Biology creates many new analysis challenges. Since high-throughput experiments are frequently conducted for the sake of discovery rather than hypothesis testing, and due to the sheer amount of measured variables they entail, it is very difficult to interpret their results. Moreover, since the goal of many experiments is to uncover bio-chemical and functional information about genes and proteins, there is an obvious need to understand the linkages amongst biological entities in literature and databases which allow us to make inferences. Literature mining[16] is expected to help with those inferences; its objective is to automatically sort through huge collections of literature and suggest the most relevant pieces of information for a specific analysis task, e.g. the annotation of proteins [7]. Another application is to uncover similarities of genes according to "publication space", or the more tongue-in-cheek term "bibliome" [6].

Since literature mining hinges on the quality of the sources of literature as well as their linkage to other electronic sources of biological knowledge, it is particularly important to study the quality of the inferences it can provide. Indeed, the *Bibliome* is not just the collection of publications and annotations available; its usefulness ultimately depends on the quality of linking resources that allow us to associate experimental data with publications and annotations. Interestingly, while literature mining is receiving considerable attention in Bioinformatics, it has not been hitherto seriously validated. Towards improving this situation, we present here our large-scale testing and comparison of literature mining algorithms, *paired* with specific bibliome resources.

In a previous study[14,12], we tested how well the Pfam protein sequence family classification[18] can be replicated from independently mining PubMed as indexed by the MeSH keyterm vocabulary. Here, in addition to presenting a general method for testing bibliome resources and literature mining algorithms, we expand on these results by testing and comparing additional bibliome resources such as GO annotations and text extracted from PubMed abstracts, as well as additional prediction algorithms, including a method based on Shannon's entropy, to combine results from different bibliome resources.

## 2. From Text Mining to the Bibliome: Looking for a "Gold Standard"

There exists extensive cross-linkage amongst biomedical databases which can be exploited for bioinformatics analysis. For instance, gene chip identifiers can be linked to protein entries in SWISSPROT which in turn can be linked to PubMed documents. Furthermore, documents are typically indexed by semantic informa-

tion about their content, including keywords and other types of annotations such as: Medical Subject Headings (MeSH), the Gene Ontology (GO), PubMed abstract text, the HUGO Nomenclature for human genes, etc. Therefore, in order to fully capture the potential of the bibliome for analysis, integration and dissemination of biological knowledge, in addition to research on text mining and natural language processing, literature mining needs more research on the quality of links amongst the resources that make up the bibliome. Text Mining is particularly applicable to the discovery of relevant information inside text — e.g. discovering a portion of text in a document most appropriate to annotate a given protein [7]. But given the highly cross-linked nature of the bibliome, we need to emphasize on the joint application of Information Retrieval (IR) and Text Mining.

Several research groups have been exploiting the cross-linked nature of the bibliome, particularly with semantic annotations such as MeSH and GO, for instance the systems developed by Masys et al [11] and Jenssen et al [9] for identifying sets of keyterms associated with sets of genes. Tools that are similar in spirit are PubMatrix [2], MedMiner [20], MeshMap [19] and others. While these systems are potentially very useful, the quality of their results has not been thoroughly validated. For instance, we have applied Latent Semantic Analysis (LSA) to discover functional themes [13,12] from the literature for microarray experiments dealing with the response to human cytomegalovirus infection. Though the functional themes we discovered matched our previously published manual annotation of the same experiments [3], and even uncovered novel functional themes[13,12], such validation by a few expert biologists is done a posteriori without access to a "*gold standard*".

By "gold standard" we mean a standardized test data which allows us, unambiguously, to decide if a given inference is correct. Homayouni et al were able to build such "gold standard" for evaluating the performance of LSA, but only by focusing on a very small set of genes [8]. Unfortunately, for data-driven experiments there is no clear expectation of what functional associations are to be found. Therefore, bibliome tools are typically tested by sampling some of their output and presenting it to experts. The problem is that experts typically disagree or cannot be an expert on all the topics involved. Even more systematic approaches such as Biocreative [7] suffer from variability in experts' opinions or experts who get tired of manually testing the output of mechanic algorithms, leading to potentially unreliable answers.

## 3. Large-scale standard for bibliome informatics: Methods and Data

### 3.1. *A general large-scale bibliome informatics test*

The first requirement for our testing methodology is the existence of a biological classification $\mathcal{C}$, accepted as a true standard, and defined on a large set $P$ of bio-

logical entities $p$ (e.g. proteins or genes), where each entity $p$ is associated with a single class $C(p)$. Given that the Bibliome is defined not only by publication and annotation resources, but also by their linkage, we also need a high-quality linking resource $L_D$ between $P$ and the documents of some publication or annotation resource $D$ — where $L_D(p)$ denotes the set of documents of $D$ associated with entity $p$. Given a $\mathcal{C}$ and $L_D$, our *large-scale bibliome informatics test* (LSBIT) can be applied to any pair, $\langle A, K_D \rangle$, of classification algorithm $A$ and keyterm set $K_D$ extracted from $D$ — where $K_D(p)$ denotes the set of keyterms that index documents $L_D(p)$ [a]. The objective of the LSBIT is then to **establish how well a given algorithm $A$ can discover a known classification $\mathcal{C}$ of biological entities $P$, from a publication resource $D$ using an associated keyterm set $K_D$ and a bibliome linking resource $L_D$ between $P$ and $D$ .**

### 3.2. *Bibliome Resources*

#### 3.2.1. *Defining $\mathcal{C}$ and $L_D$*

We chose the Pfam protein sequence classification [18] as $\mathcal{C}$ for our tests. Pfam is a manually curated collection of protein families, currently encompassing several thousands of families. The proteins of the same Pfam family are very similar in sequence, which typically leads to functional similarity. Pfam is an ideal classification for objective evaluation and comparison of Bibliome informatics due to its being based on a physical property of proteins (sequence) which typically leads to functional similarity. Having settled on Pfam for our classification standard $\mathcal{C}$, our biological entities $P$ are proteins. Therefore, a most appropriate linking resource $L_D$ to test $\langle A, K_D \rangle$ with is the SWISSPROT (now UNIPROT [17]) database, which is a protein sequence database curated by experts. Besides the amino acid sequence of a protein it also lists different types of annotations, cross-references to other databases (including the Pfam family of a protein), as well references to relevant publications for each protein. Therefore, the LSBIT with $\mathcal{C}$ = Pfam and $L_D$ = SWISSPROT, can be applied to classify proteins $p$ under various pairs $\langle A, K_D \rangle$. The expert nature of Pfam and SWISSPROT allows us to use them as a standard for the classification of proteins.

However, before the LSBIT may be performed, some preprocessing of the set of proteins to be tested is necessary. We extracted all the SWISSPROT protein IDs which contained a single Pfam classification. Multiple Pfam family assignments occur for 15% of all SWISSPROT proteins, possibly because some proteins have more than one classified domain. Because we are interested in constructing a large, unambiguous data set for validating bibliome methods, we removed multi-

[a] We use keyterm to refer to both keywords and keyphrases depending on available resources.

classification proteins. We do not consider those to be erroneous in any way, but they simply do not serve the purposes of out testing standard, which needs to be unambiguous. After pre-processing (details in [12,14]), we obtained a dataset with $|P| = 15,217$ proteins from $\mathcal{C} = 1611$ Pfam families. Each protein $p$ is associated with a unique Pfam family $C(p)$.

#### 3.2.2. *Defining publication/annotation resources $D$*

Since SWISSPROT lists PubMed IDs, a very natural publication resource is PubMed; let us denote it as $D_{PM}$. Via SWISSPROT, our linking resource $L_D$, we retrieve different keyterm sets $K_D$ from PubMed, detailed in the next subsection. Another annotation resource we used was GO, which we denote as $D_{GO}$. This was done via another bibliome resource: the GOA/UNIPROT dataset provided by the GOA project, run by the European Bioinformatics Institute (EBI). Because we needed to compare and integrate the tests using $D_{PM}$ and $D_{GO}$, we looked at a reduced set of proteins for which links to both PubMed publications and GO annotations were found, that is $P^r = \{p : L_{D_{PM}}(p) \bigcap L_{D_{GO}}(p) \neq \emptyset\}$. We also restricted our study to Pfam families with at least 3 proteins. This reduced dataset $P^r$ contains 3663 proteins from 618 distinct Pfam families. 179 of families contain only 3 proteins; the largest 3 families contain 17 proteins. Mean and median family size is 5.9 and 5 proteins, respectively; standard deviation is 3.3.

### 3.3. *Keyterm Sets $K_D$ to Test*

We have adapted the IR vector space model [1] to represent proteins as vectors in a keyterm space. Four different keyterm sets were used in our analysis. Three of these sets contain keyterms extracted from PubMed ($D_{PM}$) publications associated with proteins, while the fourth was based on term annotations in the Gene Ontology ($D_{GO}$). The first keyterm set $K^{MeSH}_{D_{PM}}$ contains MeSH terms. MeSH (Medical Subject Headings) is a hierarchically organized vocabulary produced by the National Library of Medicine to index MEDLINE/PubMed. $K^{MeSH}_{D_{PM}}$ contains all MeSH terms occurring in the $L_{D_{PM}}(p)$ set of PubMed records associated with all proteins $p \in P^r$.

For the second keyterm set, $K^{Words}_{D_{PM}}$, we used all words (after stop-word filtering) extracted from PubMed abstracts associated with all proteins $p \in P^r$. To build the third keyterm set, $K^{Stems}_{D_{PM}}$, we reduced the words in $K^{Words}_{D_{PM}}$ to their linguistic stems, using a morphological normalization tool, called BioMorpher, which we have used previously[21]. Finally, the fourth keyterm set $K^{Terms}_{D_{GO}}$ contains terms from the $L_{D_{GO}}(p)$ set of GO annotations associated with all proteins $p \in P^r$. Notice that many of the annotations in GO are electronically inferred (e.g. they are based on hits from sequence similarity searches or are transferred

from database records). To avoid circularity in our argument we used the GO evidence code to filter out term annotations inferred from electronic annotations (IEA), limiting our selection to those annotations assigned due to experimental evidence or published literature.

For each of these keyterm sets, we compute a protein-keyterm co-occurrence matrix (details below) where each positive entry denotes that the respective keyterm occurs in a document or annotation linked to the respective protein. The rows of the Matrix define the protein vectors for each protein $p \in P^r$ in the respective keyterm space. Table 1 summarizes the number of non-zero entries for each matrix and the average number of keyterms per protein in each of the four keyterm sets.

Table 1. A comparison of the four keyterm sets.

| | $K_{D_{PM}}^{MeSH}$ | $K_{D_{PM}}^{Words}$ | $K_{D_{PM}}^{Stems}$ | $K_{D_{GO}}^{Terms}$ |
|---|---|---|---|---|
| total protein-keyterm associations | 98707 | 560639 | 484072 | 14583 |
| avg. keyterms per protein | 27 | 153 | 132 | 4 |

### 3.4. *Protein Vectors and Protein Similarity*

The entry for a given protein-keyterm pair in the protein-keyterm matrix co-occurrence is a weight representing the relative importance of the keyterm for that protein. This weight is defined by multiplying a local and a global weight for the protein-keyterm pair. The local weight is the *term frequency* $tf_{ik}$, defined as the number of documents or annotations cited for protein $p_i$ in SWISSPROT that are also indexed by keyterm $k$ in publication resource $D$ being tested.

The coefficients of the protein vectors are then scaled by a global weight to capture the relative importance of each keyterm in the space. The global weight we applied is related to the *Inverse Document Frequency* (IDF) in IR [5]. We named it *inverse protein family frequency* (IPFF) and defined it as $ipf f_k = \log(\frac{N^{PF}}{n_k^{PF}})$ where $N^{PF}$ is the total number of Pfam families in $\mathcal{C}$ and $n_k^{PF}$ is the number of Pfam families that contain a protein with at least a document/annotation indexed by keyterm $k$. Finally, the new protein-keyterm co-occurrence matrix $W$ is defined by $w_{ik} = tf_{ik} \cdot idf_k$ where row $i$ denotes protein vector $i$ in keyterm dimension/column $k$. Figure 1 depicts this process.

To measure how similar two proteins are in keyterm space, we used the IR cosine measure [1]: given protein vectors $\mathbf{p}_i$ and $\mathbf{p}_j$ in a $n$-dimensional keyterm space, the cosine similarity $\sigma_{\cos}$ between them is given by the normalized dot product:

$$\sigma_{\cos}(\mathbf{p}_i, \mathbf{p}_j) = \frac{\mathbf{p}_i \cdot \mathbf{p}_j}{\|\mathbf{p}_i\|\|\mathbf{p}_j\|}$$

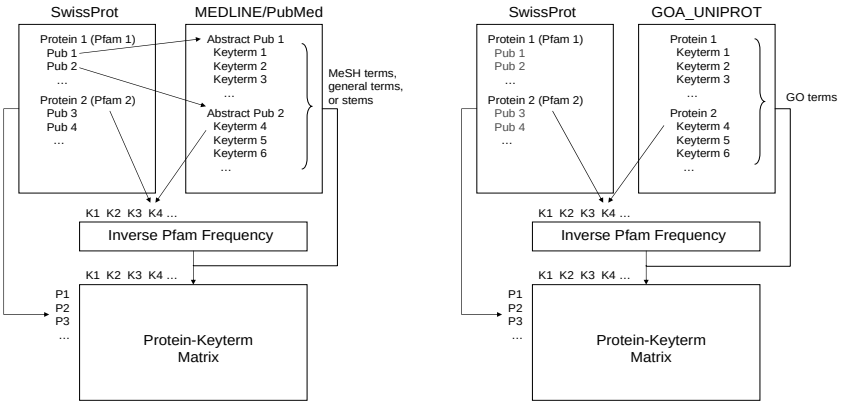


Figure 1. The process of building a protein-keyterm matrix using different linkage information sources: MEDLINE/PubMed (left) and GOA_UNIPROT (right)

### 3.5. *Prediction Algorithms $A$*

Our first LSBIT experiments, designed to establish how well we can predict the Pfam family of proteins using the bibliome resources described above, tested two classification algorithms closely related to the $k$-nearest neighbor algorithm [4]. Given a protein keyterm vector $\mathbf{p}_i$ and an angle $\alpha$, the first algorithm, $A_\alpha$, assigns a score to each Pfam family $j$ based on the number of proteins of that family found in a hypercone defined by the angle $\alpha$ and centered around $\mathbf{p}_i$, as illustrated in figure 2(a). Thus, $A_\alpha$ returns a ranking of Pfam families based on this score:

$$A_\alpha : \mathbf{Pfam}_j(\mathbf{p}_i, \alpha) = |\{\mathbf{p}_k \in pfam_j : \sigma_{\cos}(\mathbf{p}_i, \mathbf{p}_k) \geq \cos(\alpha)\}|$$

The family with most proteins in the neighborhood is ranked first, and so forth. This algorithm is described in detail in [12,14].

A problem with the $A_\alpha$ algorithm is that it depends on an angle $\alpha$. If $\alpha$ is large, unrelated proteins may be included in the neighborhood; if $\alpha$ is small the neighborhood may contain very few proteins or may be empty, in which case no prediction can be made. A second problem is that it is biased towards ranking larger families first. We have adapted $A_\alpha$ to deal with both these issues. In the new algorithm, $A_{WV}$, every protein in the space issues a "weighted vote" for its Pfam family (not just those inside a neighborhood hypercone):

$$A_{WV} : \mathbf{Pfam}_j(\mathbf{p}_i) = \frac{\sum_{\mathbf{p}_k \in pfam_j} \sigma_{\cos}(\mathbf{p}_i, \mathbf{p}_k)}{\sqrt{|pfam_j|}}$$

The weight of each protein's vote is given by the cosine of the angle between

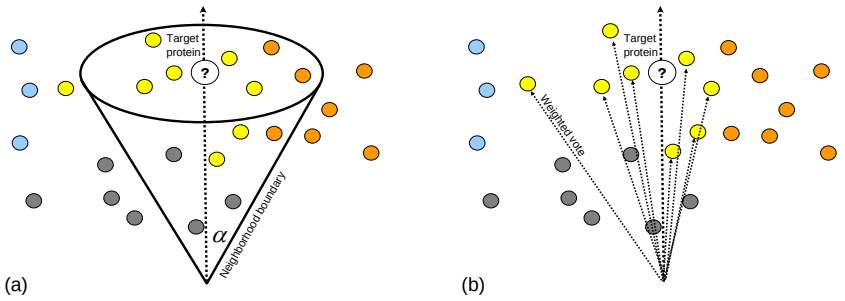


Figure 2. (a) $A_\alpha$ prediction algorithm: target protein neighborhood defined by the hyper-cone with an opening angle $\alpha$ and centered around the target protein vector . (b) $A_{WV}$ prediction algorithm: target protein and other proteins voting in proportion to their cosine similarity to the target protein.

its vector and the vector of the protein being classified. In order to weaken the bias towards larger families, the family score is normalized with a division by the square root of its size. Figure 2(b) illustrates this process. $A_{WV}$ improves on our first algorithm because it does not require a neighborhood angle to be defined in advance and it always issues a prediction for any protein vector in the space. Additionally, as we will see next, it has a higher prediction success than $A_\alpha$.

## 4. Results: Testing $\langle \boldsymbol{A}, \boldsymbol{K_D} \rangle$

The two algorithms $A_\alpha$ and $A_{WV}$ were tested using the four keyterm sets $K_{D_{PM}}^{MeSH}$, $K_{D_{PM}}^{Words}$, $K_{D_{PM}}^{Stems}$ and $K_{D_{GO}}^{Terms}$. Figure 3 shows the prediction success of our algorithms using $K_{D_{PM}}^{MeSH}$, in terms of proteins *recalled*, i.e. the number of proteins for which the Pfam family was predicted correctly. The first entry on the x-axis (labelled weighted) corresponds to the weighted-voting algorithm $A_{WV}$. The remaining entries on the x-axis (labelled 0.1, 0.2, etc.) indicate the cosine of $\alpha$ for the $A_\alpha$ algorithm. The y-axis shows the number of proteins predicted out of a total of 3663 $\in P^r$. The black, dashed curve shows the number of proteins for which a prediction was made for the respective neighborhood angle $\alpha$. As the cosine threshold increases, the number of predictions made by $A_\alpha$ decreases.

$A_{WV}$ outperformed $A_\alpha$ in all our tests, therefore for the other three keyterm sets, we only display results for $A_{WV}$ summarized in Table 2. Noticeably, the three keyterm sets extracted from PubMed records performed better than the one extracted from GO annotations. This might be due to fewer GO than PubMed keyterms per protein (see table 1). Among the three keyterm sets based on PubMed, the two obtained from abstract words significantly outperform the one

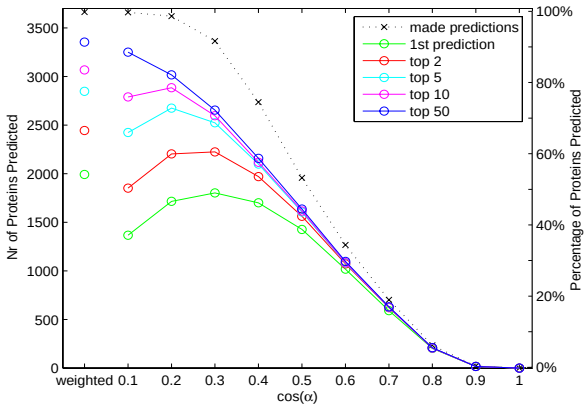


Figure 3. Prediction success using MeSH terms from PubMed publications.

containing MeSH terms; the stem-based keyterms provided slightly better results than plain words.

Table 2. Prediction success for $A_{WV}$.

| | $K^{MeSH}_{D_{PM}}$ | $K^{Words}_{D_{PM}}$ | $K^{Stems}_{D_{PM}}$ | $K^{Terms}_{D_{GO}}$ |
|---|---|---|---|---|
| 1st prediction | 54.35% | 75.27% | 75.89% | 38.08% |
| top 2 | 66.72% | 84.17% | 84.22% | 45.65% |
| top 5 | 77.70% | 88.83% | 89.30% | 55.53% |
| top 10 | 83.76% | 91.13% | 91.48% | 61.86% |
| top 50 | 91.54% | 94.02% | 94.40% | 75.59% |

## 5. Integrating Predictions from Different Keyterm Sets

We noticed that the sets of proteins correctly predicted using different keyterm sets do not completely overlap. In our analysis we found that Shannon's measure of entropy [10] can be used to measure the uncertainty associated with a prediction, and usefully exploited to combine the predictions from different keyterm spaces.

Let $\rho_K(\mathbf{p}_i, pfam_j, \alpha)$ be the probability of selecting $pfam_j$ as the protein family predicted for protein $\mathbf{p}_i$ using keyterm set $K$ and a neighborhood bounded by angle $\alpha$. We estimate this probability as follows:

$$\rho_K(\mathbf{p}_i, pfam_j, \alpha) = \frac{|\{\mathbf{p}_k \in pfam_j : \sigma_{\cos}(\mathbf{p}_i, \mathbf{p}_k) \geq \cos(\alpha)\}|}{|\{\mathbf{p}_k : \sigma_{\cos}(\mathbf{p}_i, \mathbf{p}_k) \geq \cos(\alpha)\}|}.$$

Then, we compute the entropy of a prediction for protein $i$ as follows:

$$H_K(\mathbf{p}_i, \alpha) = \begin{cases} \infty & \text{if } |\{\mathbf{p}_k : \sigma_{\cos}(\mathbf{p}_i, \mathbf{p}_k) \geq \cos(\alpha)\}| = 0 \\ -\sum_j \rho_K(\mathbf{p}_i, pfam_j, \alpha) \log \rho_K(\mathbf{p}_i, pfam_j, \alpha) & \text{otherwise.} \end{cases}$$

Finally, we compute the prediction uncertainty of protein $i$ using keyterm set $K$, $U_K(\mathbf{p}_i)$, as the average entropy on a finite set of angle thresholds $T$:

$$U_K(\mathbf{p}_i) = \begin{cases} \infty & \text{if } \forall\, \alpha \in T, H_K(\mathbf{p}_i, \alpha) = \infty \\ \langle H_K(\mathbf{p}_i, \alpha) \rangle & : \alpha \in T \wedge H_K(\mathbf{p}_i, \alpha) \neq \infty. \end{cases}$$

Using the uncertainty measure, we implemented and tested a novel protein family prediction algorithm that integrates predictions issued by each keyterm set. Let $\mathcal{K}$ be a set of keyterm sets. For $K \in \mathcal{K}$, let $\mathbf{Pfam}_j^K(\mathbf{p}_i)$ be the score assigned to protein family $j$ when predicting protein $i$ using keyterm set $K$. Then, our integration algorithm based on uncertainty, $A_U$ is implemented as follows:

$$A_U : \mathbf{Pfam}_j^{U_\mathcal{K}}(\mathbf{p}_i) = \mathbf{Pfam}_j^K(\mathbf{p}_i) \text{ where } K = \underset{K' \in \mathcal{K}}{\operatorname{argmin}} U_{K'}(\mathbf{p}_i).$$

As a baseline for comparison, we implemented a simple prediction algorithm, $A_{\langle K \rangle}$, that also integrates the predictions issued by the four keyterm systems by computing the average score $\langle \mathbf{Pfam}_j^K(\mathbf{p}_i) \rangle$ over all $K \in \mathcal{K}$. Table 3 summarizes the results obtained by these algorithms, highlighting the usefulness of an uncertainty-based method for the top predictions. Indeed, in addition to clearly outperforming $A_{\langle K \rangle}$, $A_U$ outperforms the best results of $A_{WV}$ with a single keyterm set ($K_{PM}^{Stems}$) (see table 2) for correct first and top 2 predictions.

Table 3. Prediction with combined keyterm sets.

| | $A_{\langle K \rangle}$ | $A_U$ |
|---|---|---|
| 1st prediction | 70.84% | 77.15% |
| top 2 | 80.02% | 84.77% |
| top 5 | 87.50% | 88.86% |
| top 10 | 91.35% | 90.88% |
| top 50 | 95.93% | 93.80% |

## 6. Discussion and Conclusions

Our experiments show that the Pfam classification of SWISSPROT proteins is quite well inferred, independently, from the publication resources and associated keyterm sets (MeSH, GO, PubMed abstracts), we tested with the LSBIT. The publication space with associated keyterms largely captures the functional information structure represented by the Pfam classification. Moreover, we have shown that Shannon's measure of entropy can be used to integrate the predictions from various keyterm sets, resulting in an improved protein Pfam prediction algorithm.

An interesting finding for us was that for all tested algorithms, protein family prediction is far superior with keywords extracted from PubMed abstracts than with words extracted from GO annotations. This suggests that although GO is becoming the standard annotation resource for gene and protein annotation, PubMed abstracts, and even MeSH keyterms, are far superior as resources for literature

mining. Given our results, it is fair to conclude that PubMed abstracts and MeSH terms contain more semantic and functional information to classify proteins. In future work, we will investigate what specific information is missing in the GO annotations which causes the lower performance.

Our results also show that the simple vector space model from IR is capable of well representing the semantics entailed in PubMed abstracts for protein family prediction: e.g. for 90% of proteins the correct Pfam family was among the top 5 ranked families (see table 2). In preliminary tests, we have observed that LSA improves the results only when using PubMed abstract words, and not with the other keyword sets. These results suggest that abstract keyterms have more synonymy and polysemy than MeSH and GO, but the details of that analysis are forthcoming. In future work we intend to produce working bibliome informatics tools that build up on the knowledge and algorithms of this study. We will also extend this study with additional algorithms and resources. This includes extending our algorithms by exploiting the Ontology nature of MeSH and GO with similarity measures, testing additional uncertainty-based methods, and methods based on our network analysis methodology [21,15].

Given the many biomedicine resources available, the bibliome as a resource for automatic functional annotation comes out strengthened from our testing methodology and experiments, as well as from our uncertainty-based integration method.

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